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Abstract

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Grant Number: 5R01LM006244-02

PI Name: ALTMAN, RUSS B.

PI Email: russ.altman@stanford.edu

PI Title: ASSOCIATE PROFESSOR

Project Title: REPRESENTING BIOLOGICAL DATA FOR MOLECULAR MODELING

Abstract: One of the fundamental goals of modern molecular medicine is to understand how the structure of biological macromolecules produces their function. The National Library of Medicine has, as one of its primary missions, the task of supporting technologies to represent, manage and manipulate information about biological structure. In the last two decades, a wealth of information has been accumulated about the structures and functions of hundreds of important molecules. The best views of molecular structure come from the high resolution structures that are widely available through the Brookhaven Protein Data Bank. The structure entries in this database typically contain links to the primary literature. These links are not crucial, however, because the structures are very well defined, and in many ways self-validating. For the majority of biological molecules, however, high resolution structures are not available. Instead, our understanding of their structure comes from multiple experimental, theoretical and statistical data sources that appear in the literature and provide important fragments of information. It is therefore critical that structural coordinate entries be tightly associated with relevant structural data (whether or not these data have been used to compute the structure or are consistent with it). The hypothesis of this work is that integrated information resources that contain both structural coordinates and the relevant available experimental data can be used to support (1) interactive evaluation of the consistency between structures and data, and (2) computation of new three-dimensional models that are maximally consistent with the available data. In order to test this hypothesis, we propose to build a system called RiboWeb. The system will focus on the structure of the 30S ribosomal subunit in procaryotes. This critical cellular component initiate the translation of mRNA into protein. It is the site of action of numerous antibiotics, and a detailed understanding of its structure would shed light on its critical function. RiboWeb will be composed of (1) a standardized representation of the primary data relevant to the structure of the 30S subunit, (2) links to the Medline references reporting these data and the special purpose databases containing ribosomal sequences and secondary structures, (3) a database of the previously proposed 305 structures, and (4) a software component that not only can test for compatibility and consistency between the primary data and the structural models, but also can compute new models based on user-specified interpretations of the primary data. Building upon our recent work in producing preliminary models of the 30S subunit, we

propose to make this resource available to our collaborators in the field of ribosomal structural biology on the internet, and to test it by Creating new models of the 30S subunit that better integrate the existing body of structural data. At the end of the grant period, RiboWeb will be a prototype for new structural information resources that tightly link coordinates with experimental (and other) data sources.

Thesaurus Terms:

biomedical resource, information system, model design /development, ribosome, structural model

Internet, RNA, computer program /software, computer system design /evaluation, nucleic acid structure, protein structure, ribosomal protein, structural biology

Institution: STANFORD UNIVERSITY
STANFORD, CA 94305

Fiscal Year: 1997

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Abstract

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Grant Number: 5R29LM005652-04

PI Name: ALTMAN, RUSS B.

PI Email: russ.altman@stanford.edu

PI Title: ASSOCIATE PROFESSOR

Project Title: MODELING AND COMPUTING WITH UNCERTAIN STRUCTURES

Abstract: In the next decade, there will be an exponential increase in the amount of information available about biological structure -ranging from the structure of organs and organisms to the structure of macromolecules. The National Library of Medicine has targeted the representation, management, and manipulation of biological structure as a key element of its mission in the next decade. Biological structure has certain attributes that make its representation and manipulation different from those of other structural domains (such as mechanical engineering). First, the variability in an individual structure over time can be quite large (be it the dynamic motion of a protein molecule, or the changing shape of a beating heart). Second, the range of structures over a population can be large, although the individual structures still share common overall features. Finally, the degree of certainty with which we can learn about biological structure is often a function of imperfect measurement techniques. Since we use our knowledge of biological structure for a variety of critically important tasks (ranging from drug design to medical treatment planning), the representation of biological structure and of that structure's variation is a particularly challenging and important task. The hypothesis of this work is that probabilistic representations of structure are sufficiently expressive to capture a wide range of structural phenomena, and are sufficiently tractable to be useful as a basis for programs that generate, modify, and analyze structure. Building on my previous work in probabilistic structure determination, I present a two-part plan to extend our understanding of structure representation and manipulation in the context of biological macromolecules. In the first part, I will study the theoretical algorithmic and implementational issues that arise when one computes with uncertain structural representations and with uncertain constraints on these representations. In the second part, I will collaborate with other scientists on a set of three important biological-structure problems that not only will provide useful primary scientific results, but also will act to ground the theoretical work in real-world problems.

Thesaurus Terms:

computer simulation, structural biology, structural model
macromolecule, model design /development
statistics /biometry

Institution: STANFORD UNIVERSITY
STANFORD, CA 94305

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